Veterinary Parasitology 213 (2015) 103–109

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Review

Susceptibility versus resistance in alveolar echinococcosis (larval infection with *Echinococcus multilocularis*)

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ARTICLE INFO

Keywords:
Alveolar echinococcosis
Resistance
Susceptibility
Regulatory T cells
TGF-beta
FGL2
PET-CT
Em18-ELISA

ABSTRACT

Epidemiological studies have demonstrated that the majority of human individuals exposed to infection with *Echinococcus* spp. eggs exhibit resistance to disease as shown by either seroconversion to parasite—specific antigens, and/or the presence of 'dying out' or 'aborted' metacestodes, not including hereby those individuals who putatively got infected but did not seroconvert and who subsequently allowed no development of the pathogen. For those individuals where infection leads to disease, the developing parasite is partially controlled by host immunity. In infected humans, the type of immune response developed by the host accounts for the subsequent trichotomy concerning the parasite development: (i) seroconversion proving infection, but lack of any hepatic lesion indicating the failure of the parasite to establish and further develop within the liver; or resistance as shown by the presence of fully calcified lesions; (ii) controlled susceptibility as found in the "conventional" alveolar echinococcosis (AE) patients who experience clinical signs and symptoms approximately 5–15 years after infection, and (iii) uncontrolled hyperproliferation of the metacestode due to an impaired immune response (AIDS or other immunodeficiencies). Immunomodulation of host immunity toward anergy seems to be triggered by parasite metabolites. Beside immunomodulating IL-10, TGFβ-driven regulatory T cells have been shown to play a crucial role in the parasite-modulated progressive course of AE. A novel CD4+CD25+ Treg effector molecule FGL2 recently yielded new insight into the tolerance process in *Echinococcus multilocularis* infection.

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1. Introduction

Alveolar echinococcosis (AE) is one of the most severe helminthic diseases, caused by infection with the metacestode or larval stage of the fox tapeworm *Echinococcus multilocularis*. Human AE first affects the liver (Stojkovic et al., 2014), with a parasite tissue continuously proliferating and infiltrating, thus forming a growing hepatic lesion that consists of a large conglomerate of parasite vesicles, which are intermingled with mainly host connective tissue and immune cells. Inflammation and immunopathology is scarce, indicating that the parasite actively modulates the host innate and immune reaction. Similar to malignant tumors, metastasis formation into other organs can take place at a later stage of infection (Vuitton and Gottstein, 2010). Due to the malignant nature with infiltrative growth and metastatic spread characteristics, AE may

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http://dx.doi.org/10.1016/j.vetpar.2015.07.029
0304-4017/

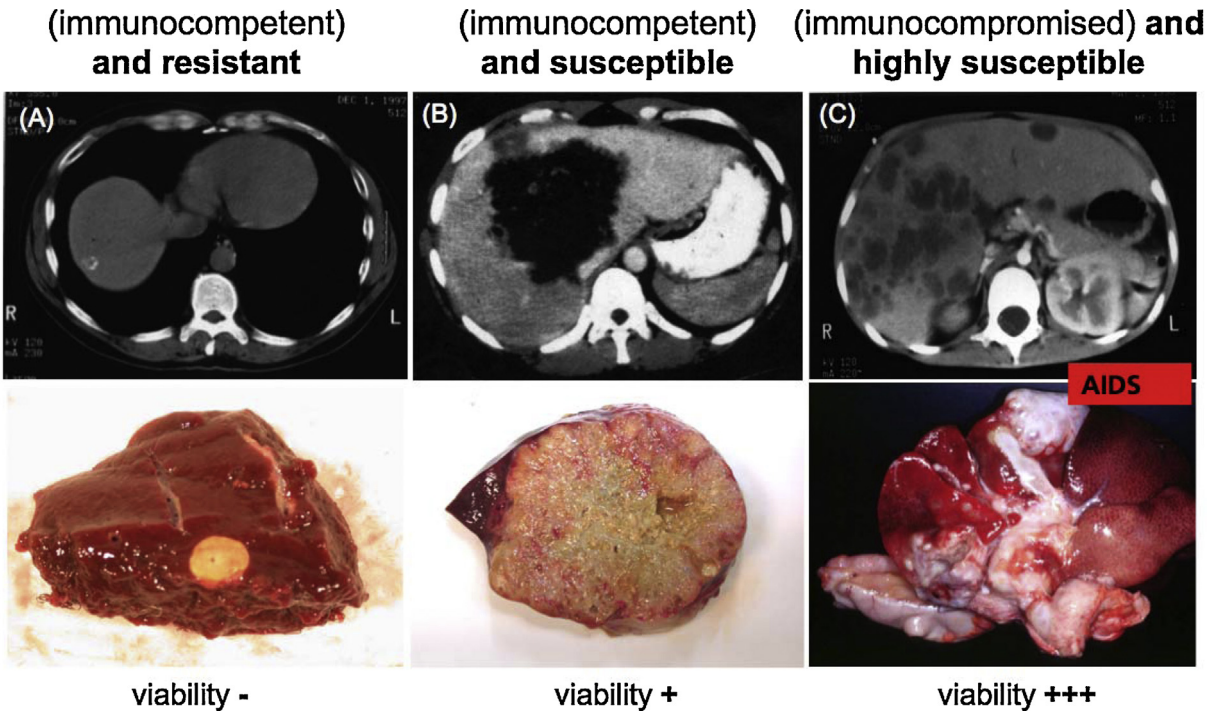

Fig. 1. Hepatic lesions formed upon *E. multilocularis* infection can be classified into the following three presentations: (A) "resistant" AE as shown by the presence of 'dying out' or 'aborted' metacestodes; (B) controlled susceptibility as shown by a slowly growing metacestode tissue — this group refers to immunocompetent AE patients, and (C) uncontrolled hyperproliferation of the metacestode due to an impaired immune response, including AIDS or other immunodeficiencies, e.g. following orthotropic liver transplantation. Upper picture line presents typical CT features of the three classes; lower picture line shows typical native liver lesions as presenting after surgery.

cause premature death in advanced stages. However, in Europe, thanks to life-long administration of the benzimidazoles albendazole and/or mebendazole in those patients who cannot benefit from radical surgical resection of the lesions, i.e. two third of patients, it has become a chronic disease, with significant impairment of quality of life. Numerous complications occur in these patients, including biliary obstruction with jaundice, septicaemia due to repeated cholangitis and bacterial super-infection of necrotic cavities in the lesion, portal hypertension, chronic Budd-Chiari disease, secondary biliary cirrhosis, as well as stroke, pulmonary complications, and a variety of diseased conditions related to distant metastases (Stojkovic et al., 2014).

Radical surgical removal of hepatic lesions is the optimal treatment option, but is feasible in only about 30% of the patients (Stojkovic et al., 2014). In advanced stages of AE, surgery is often incomplete due to the diffuse infiltration of metacestode tissue into non-resectable structures or sites. The currently available chemotherapy, based on the benzimidazole derivatives albendazole and mebendazole, has clearly increased the life expectancy of affected patients, and was shown to be effective in 55–97% of AE cases (Torgerson et al., 2010; Piarroux et al., 2011; Stojkovic et al., 2014).

Epidemiological studies have demonstrated that the majority of human individuals exposed to infection with *E. multilocularis* eggs exhibit resistance to disease as shown by either seroconversion to parasite-specific antigens and maintenance of a seropositive status, and/or the presence of 'dying out' or 'aborted' metacestodes (Rausch et al., 1987; Bresson-Hadni et al., 1994; Romig et al., 1999; Gottstein et al., 2001). For those individuals where infection leads to disease, the developing parasite is partially controlled by host immunity: in the case of immunocompetence, a slowly growing metacestode is observed, referring to that form of AE where first clinical signs appear years after infection. In the case of impaired immunity, caused by AIDS, other immunodeficiencies or immunosuppressing therapies such as following organ transplantation, cancer chemotherapy, or chronic inflammatory diseases, an uncontrolled proliferation of the metacestode is observed, leading to a more rapidly progressing disease status (Chauchet et al., 2014).

One of the frequently encountered questions raised by clinicians is, how many people infected with *E. multilocularis* eggs will effectively develop disease (AE) (→ see Fig. 1b), and how many exhibit resistance to disease; and among the infected "resistant" individuals, how many present early abortion of infection (i.e. no lesion detectable at all) and how many present spontaneous late abortion (i.e. fully calcified lesions still detectable by imaging procedures) (→ see Fig. 1a). So far, only a very rough approach to answer these questions can be attempted, i.e. based on the following reflections:

In the study of Gottstein et al. (2001) carried out with healthy Swiss blood donors living in a hyperendemic area of Switzerland, a rounded seroprevalence of 0.2% was found (Table 1), using a highly specific serological test (Em2-ELISA: 99% specificity in Gottstein et al., 1993; 100% specificity in Gottstein, 1989). In Switzerland, for the same time period, the annual incidence was 0.2 AE cases per 100,000 inhabitants, which equals 0.0002% in percent of the population. As AE-experts repeatedly stated that the time interval between infection (=plus/minus time-point of seroconversion) and diagnosis of symptomatic disease ranges between 5 and 15 years (mean 10 years), we can correct the annual case incidence by a factor of 10, so as to merge both serological and clinical baselines.Based on this theoretical approach (serological prevalence of 0.2%, corrected clinical prevalence of 0.002%), one can conclude that from 100 AE-seropositive people, only one person will develop disease, and the other 99 will appear as "resistant" to disease. The subsequent question on how many seropositive resistant individuals will present hepatic "died-out" lesions, and how many will remain "negative" in any imaging aspects, one can again use the work of Gottstein et al. (2001) to perform a rough estimation: In this

Table 1
Epidemiological studies investigating selected human populations for infection with *E. multilocularis*. Serological screening was combined with imaging procedures. Each study was differently designed, and the serological tools used were not standardized; thus comparison of findings can only be relied on a few basic parameters. For serology, we selected the Em2-ELISA as consistent used in all of the studies included in this table.

Study	Group investigated	No. of people investigated	No. of AE cases	No. of abortive cases	No. of Em2-seropositive inapparent cases[a]	Ratio of abortives versus Em2-positives plus abortives (in %)
Gottstein et al. (1987)	Healthy blood donors, Switzerland	17,166	2	[b]	4	–
Bresson-Hadni et al. (1994)	Selected population at risk, France	7,884	8	5	49	9
Romig et al. (1999)	Selected population at risk, Germany	2,560	1	2	9	18
Gottstein et al. (2001)	Healthy blood donors, Switzerland	2,943	0	1	3	25
Bartholomot et al. (2002)	Selected population at risk, China	2,482	84	451	[c]	–

[a] Initial seropositivity was confirmed by subsequent investigations, and lack of AE lesion formation was confirmed by appropriate imaging procedures.
[b] In 1987, clinical imaging did not yet know about the occurrence of abortive AE cases, thus respective documentation is lacking.
[c] Serology was not consistently carried out with all study participants.
1Experimental primary infection in the murine model showed that mice seroconverted approximately between 9 weeks (Matsumoto et al., 2010) and 8 weeks (Pater et al., 1998) after peroral egg infection For the present calculation, we assumed that every infected person who subsequently developed AE also serocoverted, as evidenced by the high serodiagnostic sensitivity of *E. multilocularis* tests. We have to mention that we do not know how many people living in an endemic area actually ingest infective parasite eggs without subsequent seronversion and parasite development. Such people are considered as innate resistant, and can, by definition, not be included in an estimative approach as done here.

study, 4 AE-seropositive blood donors were detected that underwent subsequently multiple imaging follow-up investigations of their liver. One (25%) of these four people presented a typical small and fully-calcified lesion (indicative for a died-out, aborted AE), while the three other *E. multilocularis* seropositive individuals remained repeatedly "negative" by ultrasonography (US) and computed tomography (CT) for multiple following years. As shown in Table 1, relatively similar findings were reported in a French study (Bresson-Hadni et al., 1994), where 9% (5 out of 54) *E. multilocularis* seropositive individuals presented abortive lesions, and in another German study (Romig et al., 1999), 18% (2 out of 11) of the seropositives were considered abortive cases. Combining the four European studies listed in Table 1, one can summarize that within a population of 30,553 people tested, 11 active asymptomatic AE cases were determined (asymptomatic AE-prevalence 0.04%), plus 8 cases of abortive (=late resistant cases) *E. multilocularis* infections ("abortive" prevalence 0.03%), and an additional 65 cases (Em2-seroprevalence 0.2%) of seroconversion following a very likely *E. multilocularis* infection without subsequent parasitological and clinical development of AE (=early resistant cases). Interestingly, the overall seroprevalence of 0.2% of all studies combined matches that of the Swiss study used above to estimate the disease occurring.

Conclusively, we can postulate that approximately 4 out of 5 AE-seropositive "resistant" people do not develop any visible hepatic lesion (i.e. early stage resistance or "AE-abortion"), while one out of 5 people will "abort" only at a later stage, allowing an initial (presumably asymptomatic) lesion formation that subsequently aborted and led to the formation of one or more calcified structures apparent in US and/or CT (Rausch et al., 1987; Bresson-Hadni et al., 1994; Gottstein et al., 2001). Although this calculative approach to answer some of the key questions of susceptibility versus resistance remains at a very rough and descriptive level, we are convinced that it approximately reflects the situation in the field, and respective conclusions may be of preliminary value for clinicians dealing with diagnostic and epidemiological aspects of AE. Based on our reflections on the matter, we invite epidemiological AE specialists to take care of these considerations and to develop appropriate mathematical approaches to provide a more scientifically based documentation of the ratios between the different forms of *E. multilocularis* infection in humans.

2. Biology and immunology of susceptibility versus resistance in AE

In infected humans, the *E. multilocularis* metacestode (larva) develops primarily in the liver. In immunocompetent individuals, a granulomatous host reaction surrounds the metacestode, including a vigorous synthesis of fibrous and germinative tissue. Depending on the type of immune response elicited by the host, infections will have different outcomes (Fig. 1): (i) seroconversion takes place, but the parasite fails to establish chronic infection, and either no lesions, or only "dying" or "aborted" lesions are detected; (ii) seroconversion takes place, and metacestodes grow slowly and establish a chronic infection, and first clinical symptoms occur putatively after 5–15 years post-infection, and (iii) uncontrolled and rapid metacestode proliferation, as it occurs in individuals with impaired immunity such as AIDS patients or patients undergoing transplantation or being treated by immunosuppressive drugs or biological agents.

Human patients suffering from chronic AE exhibit a rather Th2-dominated immunity associated with an increased susceptibility to disease. In contrast, a Th1-biased immune response induces protective immunity, which may even lead to aborted forms of infection. In most AE cases investigated, a mixed Th1/Th2 profile is found during the chronic stage of disease (Hübner et al., 2006) associated with the expression of pro-inflammatory cytokines in the periparasitic granuloma and partial/relative protective immunity (restriction of parasite growth) through fibrosis and necrosis (Bresson-Hadni et al., 1990). In terms of cytokine profiles, a Th2- or anti-inflammatory-associated response, respectively, against *E. multilocularis* in the immunocompetent but still susceptible host encompasses high production of IL-5 (Sturm et al., 1995) and IL-10 (Godot et al., 1997; Dreweck et al., 1999), respectively, while in relatively resistant hosts the Th1-cytokine profile is dominated by IFN-α (Godot et al., 2003) and IL-12 (Emery et al., 1998) as initiating cytokines, and IFN-γ (Liance et al., 1998) and TNF-α (Amiot et al., 1999; Shi et al., 2004) as effector cytokines. Recently, the discovery of the IL-17 cytokine family has added a new dimension to the balance of inflammation and tolerance during parasitic infections. A recent study involving human AE patients showed that increased IL-17A expression was associated with protection, while upregulation of IL-17F expression might contribute to both

protection and pathogenesis (Lechner et al., 2012). IL-10 (Harraga et al., 2003) was found to be abundant in the periparasitic granuloma surrounding *E. multilocularis* metacestodes in the liver, as well as immuno-modulating TGF-β (Wang et al., 2014). Exploring TGF-β in its multiple functions in *E. multilocularis* infection is, however, still a relatively open field of research. There is evidence that TGF-β1, besides its role in immune tolerance, is an extremely potent inducer of the synthesis of procollagen and other extracellular matrix components as well as in (Bartram and Speer, 2004), and has an essential role in the pathogenesis of liver fibrosis. Such mechanisms could also play an important role in AE, as fibrosis and collagenosis are hallmarks of AE-immunopathology (Wang et al., 2013; Vuitton et al., 2006; Vuitton and Gottstein 2010). The major signalling pathway for all TGF-β members is activated through ligand binding to a cell-surface receptor complex of type I and type II serine–threonine kinases receptors; and a group of intracellular signalling intermediates known as Smads is then phosphorylated. Phosphorylated Smads translocate to the nucleus where they function as transcription factors, initiating target gene transcription (Banas et al., 2006). The relationship between the TGF-β/Smad pathway, and especially the expression of Smad7, which may play a regulatory role in the system, and clinical and/or pathological features of AE in experimental models as well as in human AE has been exploratively addressed by Wang et al. (2013) and recently also by Pang et al. (2014). Other studies on the immunopathology of AE revealed that CD4+CD25+ Treg cells play a critical role in human AE by blunting immune responses to specific antigens, or by suppressing the secretion of proinflammatory cytokines, especially through IL-10 and TGF-β1 (Hübner et al., 2006).

Mice, as the natural intermediate hosts, represent an excellent model to study the immunology of AE. Conventional experimental infection, leading to secondary AE, is performed by intraperitoneal or intra-hepatic inoculation of *E. multilocularis* metacestode vesicles. These pre-formed metacestodes are protected by the surface-associated and carbohydrate-rich laminated layer (LL) (Gottstein et al., 2002; Díaz et al., 2011). Immunocompetent mice respond immunologically, but in a strain-dependent manner (Matsumoto et al., 2010). It was shown that impairment of cellular immunity (immune suppression) in mice is followed by an increase in susceptibility to *E. multilocularis* (Baron and Tanner, 1976) and this was further confirmed in SCID mice (Playford and Kamiya, 1992) and in nude mice (Dai et al., 2004). A similar increase of susceptibility, associated with a decrease of delayed type hypersensitivity was also observed in *E. multilocularis* infected mice treated with ciclosporin, which interferes in IL-2 production by T-cells (Liance et al., 1992). Principally, upon experimental infection, immunocompetent mice elicit a cell-mediated immune response, which is so far inefficient as it impairs, but does not inhibit, the proliferation of the metacestode (Dai et al., 2004; Mejri et al., 2010). It has been shown that the type of the primary immune response toward infection, initially Th1-oriented, got progressively Th2-oriented (Mejri et al., 2011a) during the progressive growth of the metacestode, leading to the chronic stage of AE. Concomitantly, intraperitoneal dendritic cells (DCs) and T cells isolated at this late stage of infection expressed relatively high levels of TGF-β mRNA, while IFN-γ mRNA, and the surface expression of the major costimulatory molecules CD80, CD86, CD40 and the MHC class II (Ia) molecules were downregulated (Mejri et al., 2011a,b). It became evident that the intraperitoneally proliferating metacestode abrogated maturation and activation of DCs. Therefore, DCs in *E. multilocularis*-infected mice were classified as tolerogenic cells, and moreover, as cells with suppressive features based upon their high level of TGF-β-expression.

Subsequent series of experiments showed that CD4+ T cell hyporesponsiveness was associated with differentiation of Treg cells (Mejri et al., 2011a). The most widely described suppressor T cells are CD4+CD25+ T cells. At the late stage of experimental infection, a five-fold increase in CD4+CD25+ T cells in infected mice became apparent, when compared to non-infected mice (Mejri et al., 2011a). Foxp3, a marker for Treg cells, was expressed at higher levels in CD4 T cells and CD8+ T cells of AE-infected mice when compared to non-infected mice. The high expression level of TGF-β in infected mice thus seemed to largely contribute to the development of regulatory CD4+CD25+Foxp3+ T cells and CD8+CD25+Foxp3+ T cells (Mejri et al., 2011a). Tregs appear thus as key immunomodulators in murine AE, associated with impaired MØ and DC functions.

In a recent study (Wang et al., 2014), IL-4 expression could be determined very soon after primary infection of mice (2–8 days). Conclusively, Th2 markers appear to be present earlier than anticipated in previous studies.

In the frame of very recent investigations on immunomodulation in AE, the role of FGL2 (fibrinogen-like protein 2) as another key parameter in the Treg-dependent downregulation of periparasitic immunity was addressed. Principally, FGL2 is a member of the fibrinogen-related superfamily of proteins secreted by T cells, is highly expressed in Tregs, and has an important role in Treg cell effector function (Levy et al., 2000). Micro-array studies showed that FGL2 expression is significantly up-regulated in the liver of *E. multilocularis*-infected mice (Gottstein et al., 2011). Upon use of *E. multilocularis*-infected *fgl2*-deficient mice (as compared to infected WT mice), a significantly lower parasite load and a reduced proliferation activity was observed, associated with increased T cell proliferation in response to ConA, reduced Treg numbers and function, relative Th1 polarisation, and increased B cell numbers and DC maturation (Wang et al., 2015). It became also evident, for the first time, that FGL2 is involved in immune regulatory processes favoring larval helminth parasite survival, and that IL-17A contributes to FGL2 regulation. By promoting Treg cell activity, FGL2 appears thus as one of the key-players in orchestrating the immunomodulation that permits chronic AE (summarized schematic presentation of FGL2 function in Fig. 2).

3. Parasite antigens involved in host-parasite interactions

Predominantly excretory/secretory (E/S) metabolic products of the *E. multilocularis* metacestode are considered to be important key players in the host parasite interplay. A neutral glycosphingolipid of *E. multilocularis* was identified as a suppressor of human PBMCs (peripheral blood mononuclear cells) proliferation following stimulation by phytohemagglutinin (Persat et al., 1996). Huelsmeier et al. (2002) isolated novel mucin-type glycoforms from the *E. multilocularis* metacestode laminated layer. *E. multilocularis*-protoscolex-associated proteins of 62, 70 and 90 kDa and several recombinant *E. multilocularis*-proteins have all been published and discussed in view of their potential interactive biological functions (reviewed by Huelsmeier et al., 2002).

In vitro experiments using the larval stage of the parasite, coupled to genomic data (Brehm and Spiliotis, 2008; Brehm 2010) indicated that a series of evolutionarily conserved signaling molecules are able to functionally interact with corresponding host cytokines. Förster et al. (2011) demonstrated that *E. multilocularis* expresses a set of nuclear receptors, one of which (EmNHR1) cross-communicates with TGF-β signaling components. More recently, the Würzburg research group of Klaus Brehm showed that EmACT, a secreted metacestode activin, was able to induce expansion of host Treg cells, and thus appears to have an important role in immunomodulation (Nono, 2012). Another parasite factor named EmTIP, homologous to mammalian T-cell immunomodulatory protein (TIP), was detected in secretory fractions of *E. multilocularis* primary cell cultures (Nono et al., 2014). EmTIP blockade inhibited the proliferation of *E. multilocularis* primary cells and the formation

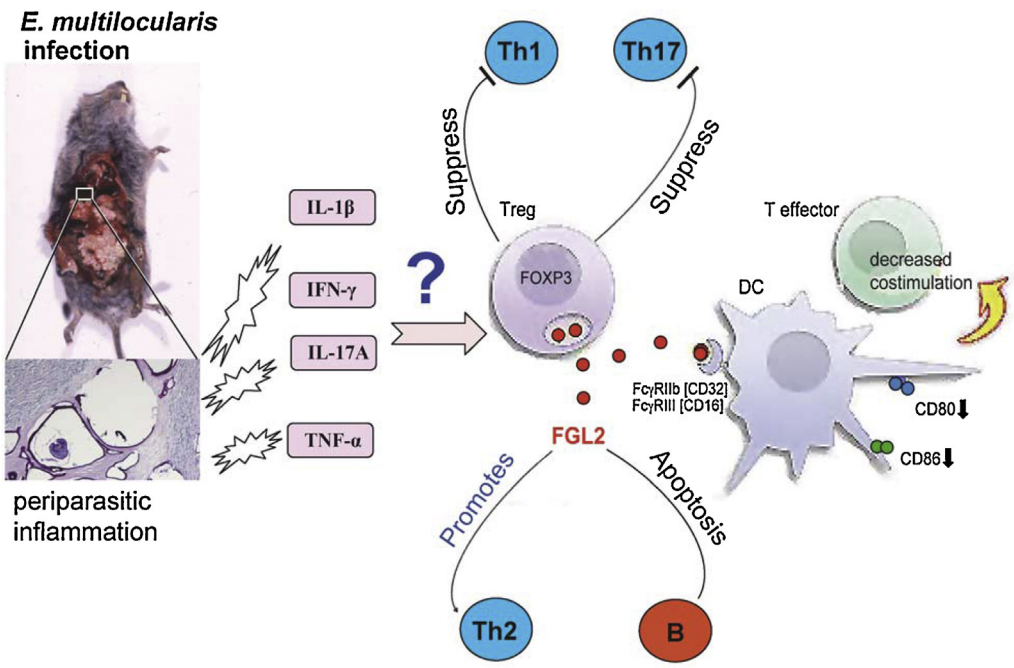

Fig. 2. The role of FGL2 in immune regulation: schematically presented hypothesis for its involvement in the host-parasite relationship. *E. multilocularis* metabolites induce release of IL-6, TNF-α, IFN-γ and IL-17; IFN-γ and IL-17A contribute to FGL2 secretion by Tregs and other cells; once FGL2 is released, it binds to FcγRIIB receptors, down-regulate the maturation of DCs, decrease co-stimulation of effector T cells, suppress Th1 and Th17 immune response, accelerate Th2 immune responses, induce apoptotic B cell death, and thus overall lead to an immune suppressed status that favours the continuous "tumour-like" progression of the parasitic metacestode.

of metacestode vesicles in vitro, suggesting that this protein is functionally important for parasite development. Also, EmTIP evoked a strong release of IFN-γ by CD4+ T-cells, hence suggesting that the secretion of this factor could "secondarily" induce a potentially protective Th1 response. Prospectively, secretory products of worms as those described above offer a novel platform for the development of safe and effective strategies for the treatment of autoimmune and/or inflammatory disorders (Pineda et al., 2014).

4. Tools to assess parasite viability in vivo

Progression of lesions, at least in immunocompetent patients, is extremely slow in AE, and a prolonged follow-up is necessary before stating about regression or progression, and especially also to assume a dying-out status of the AE lesion, which may result in abrogation of continuous medication. Calcification of lesions, and its increase which indicates efficient protective immune response with subsequent degeneration of the parasite, cannot be used only as a reliable marker of parasite death in the whole lesion (Wang et al., 2011). (18F)-fluorodeoxyglucose (FDG) is currently the unique validated tracer of AE lesions in positron emission tomography (PET); it was proposed 15 years ago to assess progression of lesions, if positive, and as a marker of parasite abortion and thus indication of benzimidazole withdrawal, if negative (Reuter et al., 1999, 2004). This approach has proved efficient in several patients, but drug withdrawal was followed by recurrence in some of them (Reuter et al., 2004; Stumpe et al., 2007). Improvement in the PET imaging procedure, better adapted to the specific situation of AE has been proposed: it is now accepted that PET may only be considered negative if images acquired 3 h (and not only 1 h) after FDG injection are negative (Caoduro et al., 2013). In fact, FDG–PET images do not directly reflect parasite viability but rather peri-parasitic host inflammatory process. The ideal PET tracer should be able to assess the course of AE upon direct uptake by the metacestode through its metabolic activity (Porot et al., 2013) or by binding to parasite molecules that are only accessible in viable metacestodes. This is supported by the fact that FDG uptake can be visualised only in those areas where the periparasitic infiltrate by immune cells is dense, and by the observation that in vitro uptake of FDG by leukocytes is far more efficient than FDG uptake by *E. multilocularis* cells or vesicles (Porot et al., 2014). Preliminary results from the retrospective comparison between MR and FDG–PET images showed that identification of micro-vesicles in AE lesions by MRI highly suggests 'metabolically active', hence viable, metacestode (Azizi et al., 2014); however, before being reliably used as a marker, studies on a larger cohort of patients with and without anti-parasite treatment withdrawal, will be necessary, as claimed by the authors.

If biopsies or fine-needle aspirates are available from AE patients, testing of parasite viability can be performed with RT-PCR upon various constitutively expressed gene targets (e.g. 14-3-3) (Diebold-Berger et al., 1997), however, limits of this method primarily relate to sampling site and methodical approach used to isolate mRNA and subsequent procedures (Ito and Craig, 2003; Matsumoto et al., 2006; Yamasaki et al., 2007). However, due to these limits, such an invasive technique cannot yet be recommended for routine follow-up. In addition to PET–CT, some specific serologic tests proved valuable to assess the efficacy of treatment of AE patients (Siles-Lucas and Gottstein, 2001; Ito and Craig, 2003). Disappearance of IgE and IgG4 isotypes of anti-*Echinococcus* specific antibodies were reported to be associated with good prognosis and absence of recurrence after surgery and chemotherapy in AE patients. This was confirmed in another series of patients, which also showed that in AE patients with progressive disease, IgG4 distinctively recognised low molecular mass antigens of Mr 26 kDa, 18 kDa, 16 kDa and 12 kDa (reviewed in Schweiger et al., 2007). In a more recent study, *E. multilocularis* metacestode-specific IgG1, IgG3, and IgE responses progressively diminished with regression from active to stable and cured AE, and IgG2 and IgG4 reactivity remained similarly high in stable and progressive cases, and lessened only with cured AE (Huang et al., 2014). However, such isotype determinations do not seem to have entered routine follow-up of AE patients, and should perhaps be evaluated further in a

larger series of patients. After successful surgery and/or chemotherapy leading to inactivation of the parasite, anti-Em18 (and to a certain extent anti-Em2+) antibodies rapidly decline, and seroconversion to undetectable levels correlates well with curative resection (Ammann et al., 2004; Tappe et al., 2010; Bresson-Hadni et al., 2011).

5. Conclusions and outlook

The response characteristics of AE-resistant people could so far not be elucidated. One already knows that impairment of Th1 cell activity is associated with a rapid and unlimited growth and dissemination of the parasite in AE, and that CD4+ recovery/reconstitution by means of appropriate therapy (such as shown in an AE-infected AIDS patient (Zingg et al., 2004), reinstated control over progression of AE treated with benzimidazoles. The remaining challenge is now to find out which type of immunotherapeutical intervention could redirect the immunity of AE patients toward improved control of metacestode proliferation. Ideally, such an intervention should lead to a "dying-out-status" of the metacestodes by matching that immune profile developed by naturally resistant people.

Acknowledgements

The elaboration of this review was supported by the Swiss National Science Foundation (31003A_141039/1), the European Commission French-Swiss InterReg IV program 'IsotopEchino' project, Bordier Affinity Products (Crissier, Switzerland) and the "Novartis Stiftung für medizinisch-biologische Forschung" no. 12A02.

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